Departement für Pferde
Abteilung Anästhesiologie
der Vetsuisse-Fakultät Universität Zürich

Direktor: Prof. Dr. med. vet. Anton Fürst

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Leitung Abteilung Anästhesiologie: Prof. Dr. med. vet. Regula Bettschart-Wolfensberger

Arbeit unter wissenschaftlicher Betreuung von
PD Dr. med. vet. Martina Mosing

# Evaluation of three tidal volumes (10, 12 & 15 mL $kg^{-1}$) in dogs for controlled mechanical ventilation assessed by volumetric capnography

**Inaugural-Dissertation**

zur Erlangung der Doktorwürde der
Vetsuisse-Fakultät Universität Zürich

vorgelegt von

**Seline Bumbacher**

Tierärztin
von Rüschlikon, Zürich

genehmigt auf Antrag von

Prof. Dr. med. vet. Regula Bettschart-Wolfensberger, Referentin
Prof. Dr. med. vet. Thomas A. Lutz, Korreferent

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**Abstract**

To the author's knowledge the recommended tidal volume ($V_T$) range (10–15 mL $kg^{-1}$) for controlled mechanical ventilation (CMV) is just empirically derived. The aim of this randomized, prospective, clinical trial was to evaluate this $V_T$-range by comparing three different $V_T$s in lung-healthy dogs under general anaesthesia with specific regard to dead space and alveolar ventilation. Ventilation variables were assessed with volumetric capnography. Each dog was randomly allocated to either a $V_T$ of 10 ($G_{10}$), 12 ($G_{12}$), or 15 ($G_{15}$) mL $kg^{-1}$ that was administered in a volume-controlled ventilation mode. The study including premedication and induction was conducted in a predefined and standardised way. Overall the data of 32 dogs was statistically analysed. There was no difference between the $V_T$-groups regarding the measured cardiovascular variables. Alveolar ventilation to body weight ratio increased and Bohr's dead space decreased in $G_{12}$ and $G_{15}$ compared to $G_{10}$ ($p < 0.001$, $p = 0.002$). Enghoff's dead space and airway dead space to tidal volume ratio decreased significantly in $G_{15}$ compared to $G_{10}$ ($p = 0.008$, $p = 0.006$). In all groups alveolar dead space was zero or negative. Mean airway pressure was indifferent between groups and peak inspiratory pressure was highest in $G_{15}$ ($p = 0.013$) but still in an acceptable range. The results of this study support the use of a $V_T$ of 15 mL $kg^{-1}$ for CMV in lung-healthy dogs without negatively impacting the cardiovascular system.

Keywords: Volumetric capnography, alveolar overdistension, canine, dead space, anaesthesia

## Zusammenfassung

Das empfohlene Atemzugsvolumen (AZV) (10–15 mL $kg^{-1}$) für die kontrollierte mechanische Beatmung (KMB) ist nach Wissen der Autorin empirisch ermittelt worden. Das Ziel dieser randomisierten, prospektiven, klinischen Studie war es, drei routinemäßig angewendete AZV bei lungengesunden Hunden in Allgemeinanästhesie zu vergleichen. Spezifisches Augenmerk galt dabei der Totraum- und alveolären Ventilation. Variablen der Respiration wurden mit der volumetrischen Kapnographie ermittelt. Jeder Hund wurde zufällig einem AZV von 10 ($G_{10}$), 12 ($G_{12}$), oder 15 ($G_{15}$) mL $kg^{-1}$ zugeteilt, welches mittels volumenkontrollierter Beatmung zugeführt wurde. Die Studie wurde unter Einhaltung eines standardisierten Protokolls durchgeführt. Insgesamt 32 Hunden wurden statistisch analysiert. Die gruppenspezifischen kardiovaskulären Variablen waren indifferent. Das Verhältnis der alveolären Ventilation zum Körpergewicht nahm in $G_{12}$ und $G_{15}$ zu und der Bohrsche Totraum ab verglichen mit $G_{10}$ ($p < 0.001$, $p = 0.002$). Der Enghoffsche Totraum und das Verhältnis des Atemweg-Totraums zum AZV nahmen in $G_{15}$ signifikant ab verglichen mit $G_{10}$ ($p = 0.008$, $p = 0.006$). Der alveoläre Totraum war in allen Gruppen null oder negativ. Der mittlere Atemwegsdruck war indifferent und der maximale inspiratorische Druck war am höchsten in $G_{15}$ ($p = 0.013$). Die Resultate dieser Studie unterstützten die Anwendung eines AZV von 15 mL $kg^{-1}$ für die KMB bei lungengesunden Hunden, ohne das kardiovaskuläre System negativen zu beeinflussen.



Schlüsselwörter: Volumetrische Kapnographie, alveoläre Überdehnung, Hunde, Totraum, Anästhesie

**Evaluation of three tidal volumes (10, 12 & 15 mL kg$^{-1}$) in dogs for controlled mechanical ventilation assessed by volumetric capnography**

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**Running title:** Different tidal volumes in healthy dogs.

## Abstract

### Objectives

To evaluate three routinely used tidal volumes ($V_T$; 10, 12 and 15 mL $kg^{-1}$) for controlled mechanical ventilation (CMV) in lung-healthy anaesthetised dogs by assessing alveolar ventilation and dead space (DS).

### Study design

Prospective, randomized clinical trial.

### Animals

Thirty-six client-owned dogs.

### Methods

Dogs were randomly allocated to either a $V_T$ of 10 ($G_{10}$), 12 ($G_{12}$) or 15 ($G_{15}$) mL $kg^{-1}$. After induction CMV was started. $PE'CO_2$ was maintained at 4.7–5.3 kPa by changing the respiratory frequency ($f_R$; $6 < f_R < 30$ breaths $minute^{-1}$). After 29 minutes cardiovascular and respiratory variables were recorded for three minutes using a multi-parameter monitor, volumetric capnography (VCap) and a blood gas analyzer. The ratios of alveolar ventilation to body weight ($VT_{alv}$ $kg^{-1}$) and airway DS to $V_T$ ($VD_{aw}/V_T$), Bohr's DS ($VD_{Bohr}$), Enghoff's DS ($VD_{BE}$) and the volume of expired carbon dioxide per breath ($VTCO_{2,br}$) were calculated. Mean airway pressure (MawP), $f_R$ and peak inspiratory pressure (PIP) were recorded. Data were analysed using one-way ANOVA and Student-Newman-Keuls tests with a statistical significance set at $p < 0.05$.

**Results**

No differences were observed for demographic data and cardiovascular variables between groups. Three dogs were excluded due to technical difficulties and one due to $f_R > 30$. $VT_{alv}$ $kg^{-1}$ ($p = 0.001$) increased and $VD_{Bohr}$ ($p = 0.002$) decreased significantly between $G_{10}$, $G_{12}$ and $G_{15}$. $VTCO_{2,br}$ ($p = 0.017$) increased and $VD_{aw}/V_T$ ($p = 0.006$), $VD_{BE}$ ($p = 0.008$) and $f_R$ ($p = 0.002$) decreased significantly between $G_{10}$ and $G_{15}$. PIP ($p = 0.013$) was significantly higher in $G_{15}$ compared to $G_{10}$ and $G_{12}$. No changes were observed in MawP.

**Conclusion and clinical relevance**

A $V_T$ of 15 mL $kg^{-1}$ is most appropriate for CMV in lung-healthy dogs without impairment of cardiovascular variables evaluated by respiratory mechanics and VCap.

**Keywords:** Volumetric capnography, overdistension, canine, dead space, anaesthesia

## Introduction

Controlled mechanical ventilation (CMV) supports the respiration of lung-healthy patients during general anaesthesia. According to veterinary literature the tidal volume ($V_T$) for CMV of lung-healthy dogs during general anaesthesia ranges from 10–15 mL $kg^{-1}$ (Hopper & Powell 2013). For decades veterinarians have adhered to those recommendations although to the authors' knowledge there is no scientific evidence whether that specific $V_T$-range is appropriate for CMV in lung-healthy dogs. A recent study showed that a $V_T$ of 8 mL $kg^{-1}$ with or without positive end-expiratory pressure (PEEP) is inappropriate to ventilate healthy anaesthetized dogs (De Monte et al. 2015).

New guidelines for long-term ventilation strategies in human anaesthesia and intensive care medicine suggest administering a low $V_T$ of 6–8 mL $kg^{-1}$ to avoid ventilator induced lung injury (VILI) (Gattinoni et al. 2010). The reason for the discrepancy between humans and dogs regarding $V_T$ needs do be elucidated and might be due to higher physiological dead space ($VD_{phys}$) in dogs (Fowler 1948; Mosing et al. 2010).

Volumetric capnography (VCap) is a tool to evaluate respiratory mechanics and dead space (DS). In VCap the exhaled carbon dioxide ($CO_2$) tension is plotted against the volume of one exhaled tidal breath (Fig. 1) (Fletcher et al. 1981). By mathematical approximation of the $CO_2$-curve, airway dead space ($VD_{aw}$), alveolar ventilation ($VT_{alv}$), physiologic dead space as well as alveolar dead space ($VD_{alv}$) and the volume of expired $CO_2$ per breath ($VTCO_{2,br}$) can be calculated (Tusman et al. 2009; Tusman et al. 2012). Airway dead space is a fraction of $V_T$ in which gas is moved by convection and not by diffusion, therefore no gas exchange takes place (Fletcher et al. 1981). In other words this is the volume of conducting airways. The alveolar dead space consists of alveoli with infinite ventilation to perfusion ratio (V/Q) (Fletcher et al. 1981; Suarez-Sipmann et al. 2014). Physiological dead space is the sum

of airway- and alveolar dead space. It therefore is the fraction of gas related to the tidal volume not participating in gas exchange. Bohr's dead space ($VD_{Bohr}$) is a non-invasively measured representation of physiological dead space and is little affected by venous admixture (low ventilation to perfusion (V/Q) ratio). Enghoff's dead space ($VD_{BE}$) can be considered as an index for global gas exchange (Enghoff 1938). In contrast to Bohr's dead space equation, the one modified by Enghoff includes the arterial tension of $CO_2$ ($PaCO_2$) and hence is depending on all causes of V/Q- mismatch (Tusman et al. 2012).

The aim of this study was to evaluate three $V_T$ (10, 12 and 15 mL $kg^{-1}$) routinely used for CMV by assessing dead space and alveolar ventilation under clinical conditions in lung healthy dogs. We hypothesised that 10 mL $kg^{-1}$ would be insufficient due to the high airway dead space volume in dogs, 12 mL $kg^{-1}$ would be most appropriate and a $V_T$ of 15 mL $kg^{-1}$ may already overinflate the alveoli and cause an increase in alveolar dead space seen by an increase in both physiological dead space variables ($VD_{Bohr}$ and $VD_{BE}$).

## Materials and methods

This randomized prospective clinical trial was reviewed and approved by the University of Zurich's Ethics Commission and the Swiss Federal Ethics Committee of Canton Zurich (ZH 289/14). Written owner consent was obtained for each dog.

### Animals

Thirty-six client-owned dogs of various breeds were included in this study. Each patient was related to a body condition score (BCS) ranging from one to nine, according to the validated world small animal veterinary association's BCS chart

(www.wsava.org/sites/default/files/Body%20condition%20score%20chart%20dogs.pdf). Inclusion criteria were a body weight ≥ 12 kg, an American Society of Anaesthesiologists (ASA) classification of one or two and no history of respiratory or cardiovascular diseases. Dogs were deemed healthy based on history and unremarkable lung- and heart auscultation in the pre-anaesthetic clinical examination. Patients were fasted overnight, but had access to water until two hours before sedation.

**Study protocol**

Dogs were randomly allocated to a group of either a $V_T$ of 10 ($G_{10}$), 12 ($G_{12}$) or 15 ($G_{15}$) mL $kg^{-1}$ (www.random.org/lists). They were premedicated with acepromazine 20 μg $kg^{-1}$ (Prequillan; Arovet SA, Switzerland) and methadone 0.2 mg $kg^{-1}$ (Methadon Streuli; Streuli Pharma AG, Switzerland) intramuscularly (IM). After 40 minutes an intravenous catheter was placed and Acetate Ringer's solution (Ringer Acetat Fresenius; Fresenius Kabi AG, Switzerland) was administered at a constant rate of 5 mL $kg^{-1}$ $hour^{-1}$. Following five minutes of preoxygenation anaesthesia was induced with propofol (Propofol 1% MCT; Fresenius Kabi, Switzerland) to effect. The largest suitable endotracheal tube (ETT) (Cuffed ETT Silicone, Smiths Medical, MA, USA) was adjusted in length, so that the proximal end was located at the level of the incisors and the distal tip at the level of the mid-neck. The ETT was connected to the anaesthetic circle system (Aespire view; GE Healthcare, Switzerland). Anaesthesia was maintained with isoflurane (Isofluran; Baxter, Switzerland) in an oxygen/air mixture. The fraction of inspired oxygen ($FiO_2$) was 0.5 with an oxygen flow between 0.2–0.3 L $minute^{-1}$. End-tidal isoflurane concentration ($F_E$´Iso) was maintained at 1.0–1.2 % and adjusted if necessary. CMV was started in a volume controlled mode with ventilator settings as follows: $V_T$ of either 10, 12, or 15 mL $kg^{-1}$ depending on the group allocation, PEEP of 4

cm $H_2O$, inspiratory pause of 20% and inspiratory-to-expiratory time ratio of 1:2. Respiratory frequency ($f_R$) was adapted with the aim to reach stable anaesthesia and ventilation variables within the first 15 minutes after induction. These were defined as: End-tidal carbon dioxide tension ($P_{E'}CO_2$) of 4.7–5.3 kPa (35–40 mmHg) and $f_R$ between 6–30 breaths minute$^{-1}$ (bpm). Exclusion criteria were a leak of > 10% of $V_T$ at any time point during the study period (verified by continuously checking the inspired- to expired volume difference on the spirometer looking at the volume-pressure curve, counterchecked by the numerous values if the loop gave the suspicion of a leak) or if 15 minutes after start of ventilation $f_R$ or $P_{E'}CO_2$ were not in the predetermined ranges. Cefazoline 22 mg kg$^{-1}$ (Kefzol; Teva Pharma AG, Switzerland) was administered intravenously (IV). Depending on the area of the surgical procedure, the patients were positioned either in sternal (S) or lateral (L) recumbency. They were prepared for surgery simultaneously and independently of data collection.

Standard anaesthesia monitoring was applied using a multi-parameter monitor (Cardiocap$^{TM}$/5; GE Healthcare, Switzerland) for ECG, pulse oximetry (peripheral oxygen saturation; $S_pO_2$) and an oesophageal temperature (T) device. Mean arterial blood pressure (MAP) was measured oscillometrically (Carescape V100 Dinamap; GE Healthcare, Switzerland).

**Volumetric capnography (VCap)**

The VCap-connector (NICO; Respironics Inc., CT, USA) consists of a mainstream $CO_2$ infrared sensor that was calibrated with ambient air before each experiment (accuracy of ± 2 mmHg) and a fixed orifice differential pressure pneumotachometer to measure flow and pressure (accuracy of ± 3%). The VCap-connector was inserted between the ETT and the breathing circuit. The recorded respiratory variables were: $f_R$, $P_{E'}CO_2$, PEEP, inspired $V_T$,

expired $V_T$, PIP, $VT_{alv}$, $VD_{aw}$, Bohr's DS ($VD_{Bohr}$), Enghoff's DS ($VD_{BE}$), $VD_{alv}$, mean airway pressure (MawP), $CO_2$ elimination per breath ($VTCO_{2,br}$) and minute ventilation ($\dot{V}_E$). The data was directly transferred to a laptop and recorded for three minutes (29 to 32 minutes after start of CMV) using a specific software (Analysis plus; Novametrix Medical Systems Inc., CT, USA).

**Measurement**

After 29 minutes a measurement period of three minutes was started. During that period the dogs were not touched to avoid any iatrogenic artefacts on the recorded variables and hence on data quality. Following variables were recorded manually once every minute: MAP, heart rate (HR), T, $SpO_2$, $f_R$ and $F_{E'}Iso$. The respiratory variables were recorded from the VCap-device as aforementioned. At minute 32 an arterial blood sample was taken anaerobically with a blood gas syringe (BD A-Line; Becton & Dickinson, Dev, UK) from either an arterial line in the dorsal metatarsal artery after discharging seven mL of blood or by direct punctuation of the artery. The blood samples were evaluated immediately for arterial partial pressure of $CO_2$ ($PaCO_2$) (RAPIDPoint 500; Siemens Healthcare AG, Switzerland). The samples were corrected for temperature. Data collection was finished after the blood sample was taken and subsequently the preparation for the surgery was completed.

**Data analysis**

The VCap-curve was computed with a custom-made macro routine in Excel (Excel; Microsoft Corporation, WA, USA) based on a curve-fitting algorithm realized by the solver function adapted from the formula given by Tusman and colleagues (Tusman et al. 2009).

VCap derived parameters were calculated from the approximated curve and the area under the curve (AUC). The raw data of three consecutive breaths from every measured minute was entered into the Excel spreadsheet, together with the $PaCO_2$ and the current local barometric pressure (Pb) (www.tecson-data.ch/zurich/tiefenbrunnen). A curve-fit volumetric capnogram (Fig.1) was calculated for each breath resulting in a total of nine analysed breaths for each dog. The variables derived from the Excel-macro were:

1. *Dead space variables (Tusman et al. 2012)*:

- Bohr's DS (Bohr 1887):

$$VD_{Bohr} = \frac{V_D}{V_T} = \frac{P_A CO_2 - P_{\bar{E}} CO_2}{P_A CO_2}$$

- Enghoff's DS: A modification of Bohr's DS (Enghoff 1938):

$$VD_{BE} = \frac{P_a CO_2 - P_{\bar{E}} CO_2}{P_a CO_2}$$

- $VD_{aw}/V_T$: $VD_{aw}$ is the volume from the beginning of expiration until the inflection point (IP) of the VCap-curve. It is normalised by $V_T$ (Fig. 1).
- $VD_{alv}$: Alveolar dead space

$$VD_{alv} = VD_{phys} - VD_{aw}$$

- $VT_{alv}\,kg^{-1}$: $VT_{alv}$ is the fraction of $V_T$ coming from the respiratory zone where gas exchange takes place (Fig. 1). It is normalised by body weight.

$$VT_{alv} = V_T - VD_{aw}$$

2. *Variables based on the elimination of $CO_2$ and $CO_2$-concentration (Fig 1)*:

- $VTCO_{2,br}$: Represents the amount of exhaled $CO_2$ with one tidal breath.

$$VTCO_{2,br} = \frac{AUC}{Pb - PH_2O}$$

AUC is the area under the curve, Pb the barometric pressure and $PH_2O$ the water vapour pressure.

- $P_ACO_2$: This is the mean alveolar partial pressure of $CO_2$ that is defined as the midpoint between IP and $P_{E'}CO_2$-value on the approximated VCap-curve.
- $P_{E'}CO_2$: Partial pressure of end-tidal $CO_2$. This is the last point on the VCap-curve before the next inspiration begins.
- $P_{\bar{E}}CO_2$: Mixed expired partial pressure of $CO_2$. Measured by dividing the area under the curve (AUC) by the tidal volume.

$$P_{\bar{E}}CO_2 = \frac{AUC}{V_T}$$

*3. Variables based on measured volume and airway pressure*:

- MawP: The VCap device directly calculated the mean airway pressure (MawP).

$$MawP = PEEP + (PIP - PEEP) * \frac{Ti}{Ti + Te}$$

As the I/E ratio was 1:2 the latter quotient is 0.33.

- $V_T$ $kg^{-1}$: Tidal volume normalised by the body weight.

**Statistical analysis**

In order to assess the minimally required amount of dogs to obtain statistically meaningful results for $VT_{alv}$ $kg^{-1}$, $VD_{Bohr}$, $VD_{aw}/V_T$ and $VD_{BE}$ between $G_{10}$, $G_{12}$ and $G_{15}$, a power analysis

was performed after the first 15 dogs (n = 5 per group). The outcome was that with a power of 0.8 and an alpha level of 0.05 an additional 18 dogs had to be included in the study.

Descriptive and analytical statistics was performed with MedCalc (MedCalc for Windows; Microsoft Corporation, WA, USA) and Excel. Data distribution was tested for normality with the Kolmogorov-Smirnov test. Statistical analysis was conducted using one-way ANOVA and ANCOVA. Significance level was set to $p < 0.05$. Normally distributed data are given as mean ± standard deviation (SD).

## Results

Four dogs were excluded from the study and the statistical analysis. Three dogs were excluded due to technical problems that led to a leak between inspiratory and expiratory $V_T >$ 10% ($G_{10} = 1$, $G_{15} = 2$) and one dog in $G_{10}$ because the exclusion criteria of $f_R > 30$ bpm was reached. The data of the remaining thirty-two dogs were statistically analysed ($G_{10} = 10$; $G_{12} = 11$; $G_{15} = 11$) (Fig. 2). The evaluated dogs (15 females and 18 males) had a body weight (BW) of 28.3 ± 11.0 kg and an average age of 6.4 ± 3.6 years. There was no difference in demographic data including BCS (Table 1). The required propofol dose for induction was between 3.5–4.2 mg $kg^{-1}$ ($p = 0.50$). In $G_{10}$ four patients were in S and six in L position. In $G_{12}$ no dog was positioned in S but eleven in L recumbency. In $G_{15}$ three dogs were in S and eight in L recumbency.

### Cardiorespiratory variables, anaesthesia and ventilation settings

No difference between groups was observed for MAP, HR, $SpO_2$ and PaCO2 (Table 1).

The settings of $f_R$, $P_{E'}CO_2$, $V_T$ kg$^{-1}$ and $F_{E'}Iso$ were within the predefined ranges. The $f_R$ was 80% higher in $G_{10}$ and 50% in $G_{12}$ compared to $G_{15}$ (Table 2).

**Dead space fraction and VCap derived variables**

The results for $VT_{alv}$ kg$^{-1,}$ $VD_{Bohr}$ and $VD_{aw}/V_T$ are illustrated in Figure 3:

The mean value of alveolar ventilation to body weight ratio ($VT_{alv}$ kg$^{-1}$) increased by 50% from $G_{10}$ to $G_{12}$ and was nearly twice as high in $G_{15}$ ($p < 0.001$). Bohr's dead space decreased in $G_{12}$ and $G_{15}$ compared to $G_{10}$ ($p = 0.002$). Airway dead space to tidal volume ratio ($VD_{aw}/V_T$) was nearly one third higher in $G_{10}$ compared to $G_{15}$ ($p = 0.006$) (Fig. 3). Alveolar dead space ($VD_{alv}$) was in all groups negative or zero for every dog therefore we did not include this variable in the statistical analysis.

The results for VCap and spirometry derived variables are given in Table 3:

$VD_{BE}$ decreased significantly with higher $V_T$. PIP was higher in $G_{15}$ compared to $G_{10}$ and lowest in $G_{12}$. Mean airway pressure (MawP) was not different between groups (Table 3).

## Discussion

Based on the results of this study a tidal volume of 15 mL kg$^{-1}$ in healthy anaesthetised dogs causes less physiologic dead space and a higher fraction of alveolar ventilation than a $V_T$ of 10 and 12 mL kg$^{-1}$. There was no evidence for the expected alveolar overdistension in the high $V_T$-group ($G_{15}$). Furthermore the measured cardiovascular parameters were not negatively affected by the different tidal volumes and remained in all groups within the physiological range. This implies that the results do not confirm our hypothesis that a $V_T$ of

15 mL $kg^{-1}$ would have shown the tendency of overinflating alveoli and that alveolar ventilation would have been best in the group receiving a $V_T$ of 12 mL $kg^{-1}$.

Several studies have shown that dead space is quite variable among healthy individuals as it is influenced by lung- and body size. Therefore the values for airway dead space and alveolar ventilation were normalised by $V_T$ and body weight, respectively, in order to compare them between groups and each individual dog (Astrom et al. 2000; Tusman et al. 2013). The normalised variables provide information about the distribution of gas in the respiratory system and the position of the airway-alveolar interface (Fowler 1948; Fletcher et al. 1981).

The most likely explanation for the decrease in the ratio of airway dead space to tidal volume is a shift in the interface between inspired and alveolar gas. The main force for the movement of air in the airway dead space is convection, whereas alveolar gas is moved by diffusion. The high respiratory frequency in the $V_T$-group of 10 mL $kg^{-1}$ decreased the time for diffusion and increased flow rate, therefore $VD_{aw}/V_T$ was higher (Fowler 1948; Thin et al. 2004). With the increase in $V_T$ the flow of the inspired gas became more turbulent and the surface area for diffusion increased. Those two circumstances together with the end-inspiratory pause for each breath and the significantly lower $f_R$ in $G_{15}$ were beneficial for diffusion and increased the fraction of alveolar ventilation (alveolar gas) (Fletcher et al. 1981). Higher tidal volumes did not increase the measured physiologic dead space variables or alveolar dead space meaning that there was no evidence for alveolar overdistension.

Gas exchange considerably improved due to higher alveolar ventilation fractions, which was evident in a significant increase in the volume of exhaled $CO_2$ ($VTCO_{2,br}$) with higher $V_T$ along with relatively constant minute ventilation between groups (Blanch et al. 2006).

A common concern is that CMV impairs the cardiovascular system and current ventilation strategies aim to prevent any hemodynamic instability (Pesenti et al. 1985). Since the measured cardiovascular variables MAP and HR remained stable between groups, there is no evidence that a $V_T$ of 15 mL $kg^{-1}$ impairs the cardiovascular system. One explanation why we did not see any impairment of a higher $V_T$ on the cardiovascular system might be that MawP did not increase. The mean airway pressure over time is the main influencing factor for the cardiovascular system as it decreases venous return due to the positive pressure in the thorax (Reller et al. 1985). Despite an increase in PIP with higher $V_T$, MawP stayed rather constant. Although MAP and HR were overall within normal limits, they are no direct measure of cardiac output and the influence of positive intrathoracic pressure on oxygen delivery. Therefore future studies should investigate the impact of a high $V_T$ on the cardiovascular system using more invasive measurements.

Spontaneously breathing lung-healthy and awake dogs have a tidal volume of approximately 15–18 mL $kg^{-1}$ compared to awake humans with a $V_T$ of 7–10 mL $kg^{-1}$ (Benchetrit 2000; Gros 2004; McDonell 2015b). The physiologic dead space in healthy dogs is approximately 60% and in humans only 30% of each tidal breath (Mosing et al. 2010; Tusman et al. 2013). We were able to confirm the high physiologic- and airway dead space in dogs. This difference in the distribution of one tidal breath in the airways and alveoli explains the discrepancy in optimal tidal volumes for CMV between dogs and humans. In lung-healthy dogs it is mostly the volume lost in the airways that is contributing to the twice as high physiologic dead space. This is also the reason, why one dog in $G_{10}$ had to be excluded due to an unacceptable high respiratory frequency, whereby $PaCO_2$ was still above the predetermined range. This shows that in lung-healthy dogs that are ventilated with low tidal volume fresh gas only reaches the conducting airways without sufficiently ventilating the alveoli.

The CMV settings in this study included a constant PEEP of 4 cm $H_2O$ to prevent atelectasis (McDonell 2015a) and ensure equal lung conditions in the dogs at the measurement period. Several studies could show that PEEP counteracts the phenomenon of collapsing and re-opening of alveoli (Richard et al. 2001). As no signs of alveolar overdistension were seen in our dogs, a PEEP of 4 cm $H_2O$ and a $V_T$ of 15 mL $kg^{-1}$ are safe to use.

One limitation of the study is that the possible influence of the body condition score on respiratory mechanics was not statistically analysed due to the low number of dogs included. Studies in humans have shown a close relation between body mass index and lung volumes (Pelosi et al. 1998). The dog with the highest PIP- (18 cm $H_2O$) and MawP value (7.5 cm $H_2O$) also had the highest body condition score (BCS = 8) and received a $V_T$ of 15 mL $kg^{-1}$, so $V_T$ might have been overestimated in this patient

Another limitation is that dogs were in different recumbency during the study period. However, we only included patients in lateral or sternal recumbency and excluded dogs in dorsal recumbency as this position causes variable changes to the lungs and the cardiovascular system (McMillan et al. 2009).

The two major mechanisms known for causing inflammation are alveolar overdistension and concurrent cyclic stretching of alveoli (Slutsky 2005). Although our results do not indicate any evidence of lung overinflation, a high tidal volume can still lead to some negative effects on the alveolar structure, especially over an extended period of time. Investigation of proinflammatory mediators in conjunction with tidal volumes of 15 mL $kg^{-1}$ would be necessary to evaluate whether higher $V_T$ lead to the development of inflammation even in lung healthy dogs (Pinheiro de Oliveira et al. 2010).

## Conclusion

In conclusion, controlled mechanical ventilation with a tidal volume of 15 mL $kg^{-1}$ resulted in better ventilatory variables in healthy dogs in a clinical setting. No impairment of measured cardiovascular parameters was observed.

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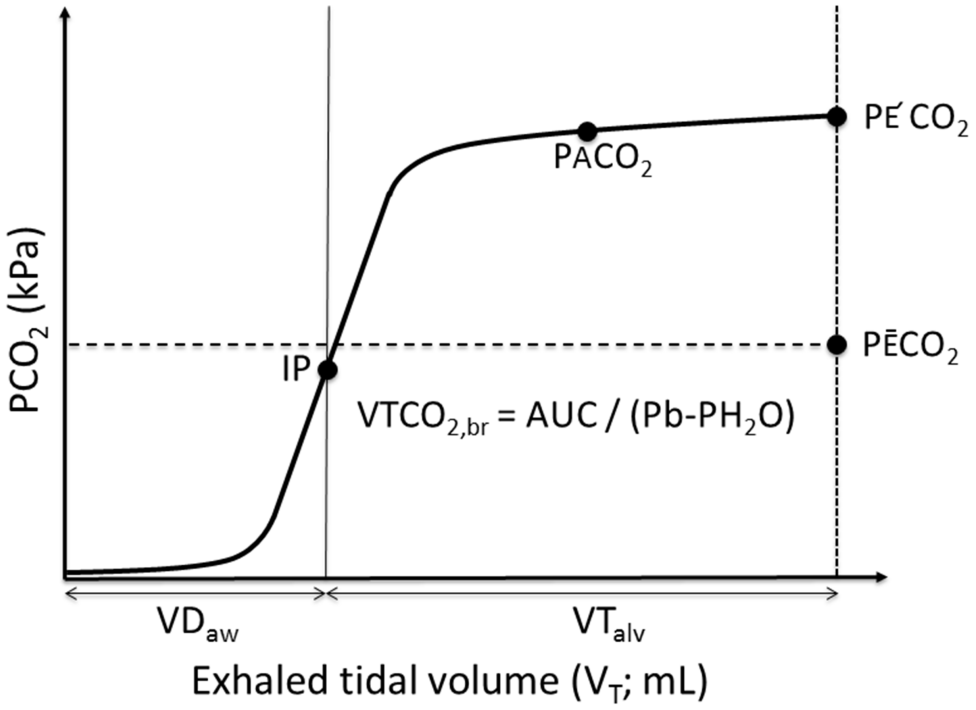


**Figure 1** Graphical plot of volumetric capnography (VCap) derived-parameters. Carbon dioxide ($CO_2$) concentration is plotted against the exhaled volume of one tidal breath. The $CO_2$-curve illustrates the volume ($VTCO_2$) and distribution of $CO_2$ in the respiratory tract. $V_T$: Tidal volume, AUC: area under the curve, IP: The inflection point divides the exhaled tidal volume in an airway- and alveolar compartment, $VTCO_{2,br}$: Volume of exhaled $CO_2$ per breath, Pb: Barometric pressure, $PH_2O$: Water vapour pressure, $PACO_2$: Pressure of alveolar $CO_2$ (midpoint between IP and $PE´CO_2$ on the VCap-curve), $PE´CO_2$: Pressure of end-tidal $CO_2$, $PĒCO_2$: Pressure of mixed expired $CO_2$.

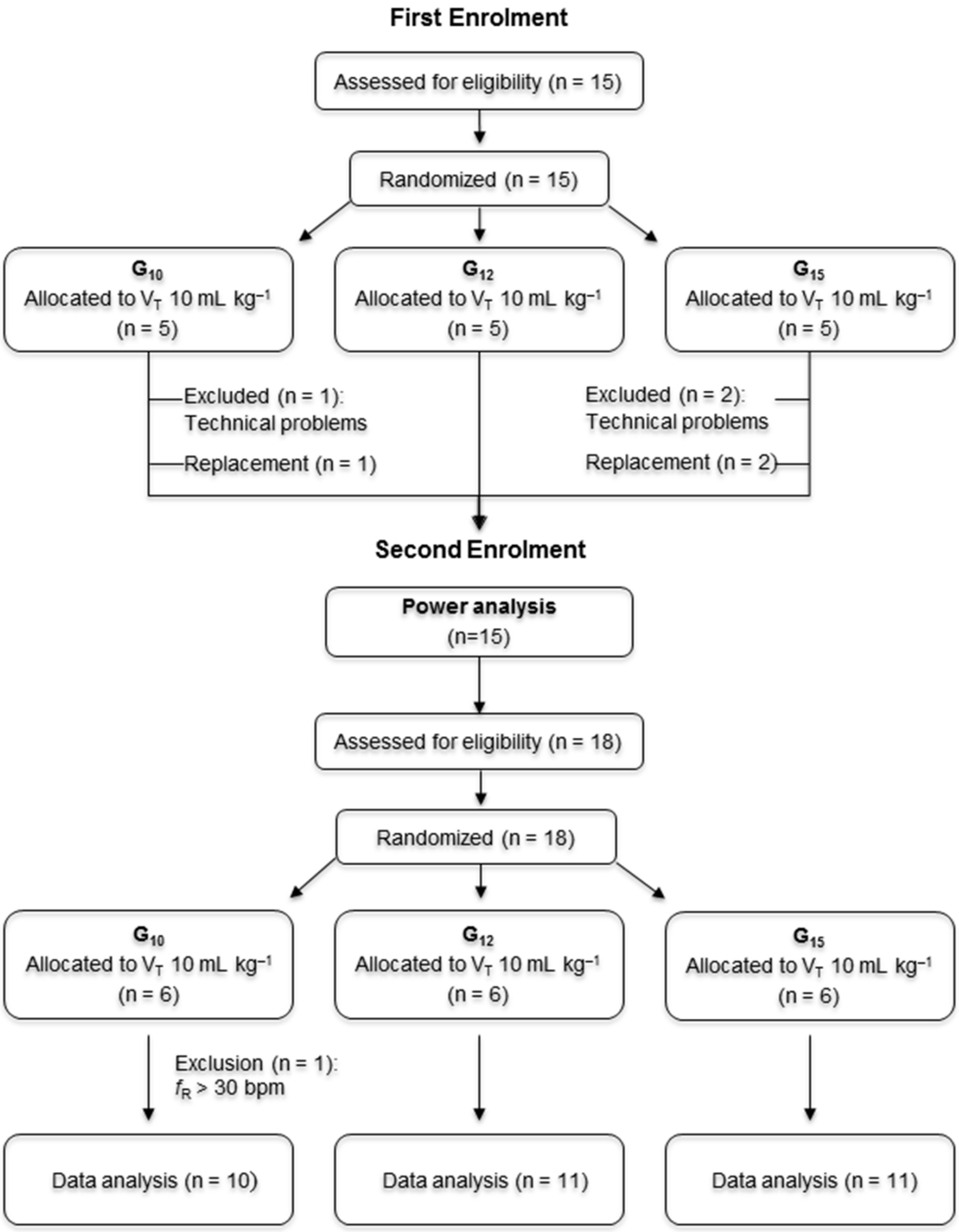


**Figure 2** Flow diagram for this study. Dogs were randomly allocated to either a tidal volume ($V_T$) of 10 ($G_{10}$), 12 ($G_{12}$) or 15 ($G_{15}$) mL $kg^{-1}$. A power analysis was performed after fifteen dogs (five per group). Additional 18 dogs were enrolled and randomly allocated to one of the three tidal volume groups.

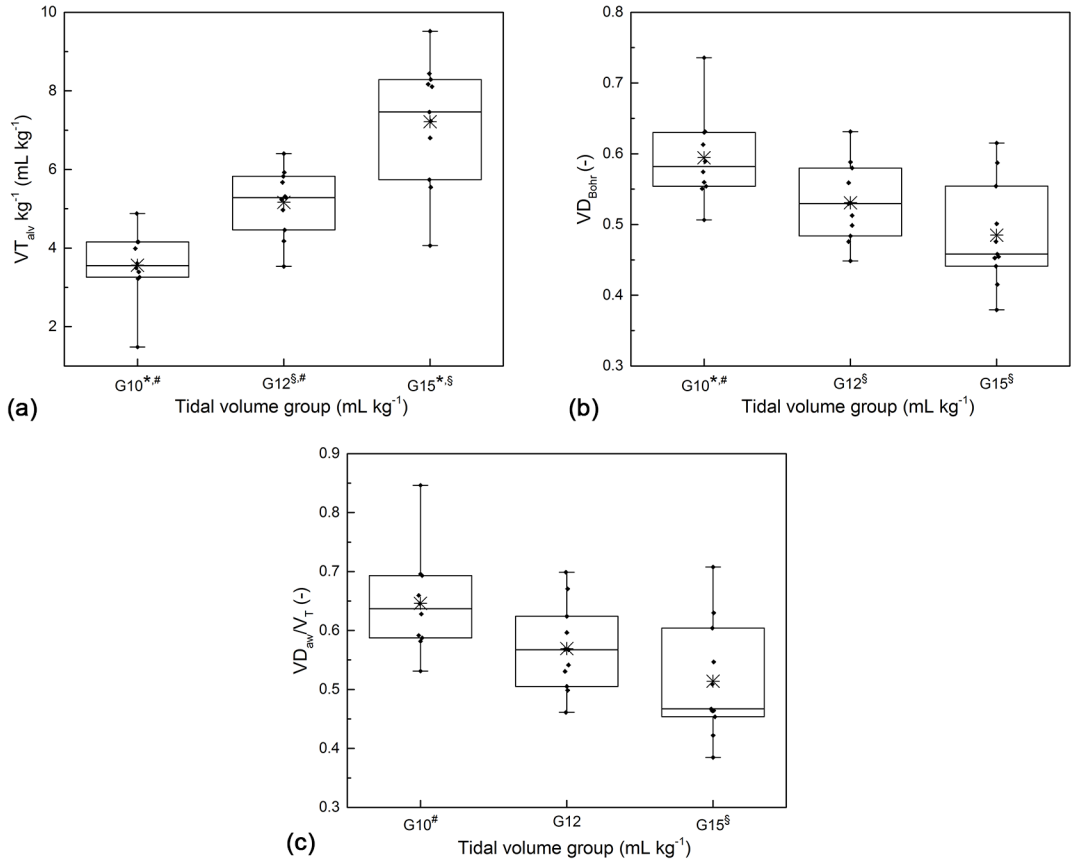


**Figure 3** Results are presented as median ± range for each tidal volume ($V_T$) group ($G_{10}$ = 10 mL $kg^{-1}$, $G_{12}$ = 12 mL $kg^{-1}$, $G_{15}$ = 15 mL $kg^{-1}$). The diagram in **(a)** shows the alveolar ventilation to body weight ratio ($VT_{alv}$ $kg^{-1}$), in **(b)** Bohr's dead space ($VD_{Bohr}$) and in **(c)** the airway dead space to tidal volume ratio ($VD_{aw}/V_T$).

§ Statistically significantly different to group 1, * statistically significantly different to group 2, ♯ statistically significantly different to group 3

**Table 1** Results (mean ± standard deviation) of cardiovascular variables and body conditioning score (BCS) in 32 lung-healthy dogs that received a tidal volume of 10 ($G_{10}$), 12 ($G_{12}$) or 15 ($G_{15}$) mL $kg^{-1}$ during controlled mechanical ventilation.

MAP, mean arterial pressure; HR, heart rate; $SpO_2$, haemoglobin-oxygen saturation in the peripheral blood; $PaCO_2$, partial pressure of arterial $CO_2$; BCS, body condition score.

| | **Tidal volume group** | | | |
|---|---|---|---|---|
| **Variables** | **$G_{10}$: 10 mL $kg^{-1}$** n = 10 | **$G_{12}$: 12 mL $kg^{-1}$** n = 11 | **$G_{15}$: 15 mL $kg^{-1}$** n = 11 | ***p*-value** |
| MAP (mmHg) | 65 ± 7 | 64 ± 5 | 64 ± 8 | 0.98 |
| HR (beats $minute^{-1}$) | 70 ± 11 | 69 ± 13 | 75 ± 21 | 0.72 |
| $S_pO_2$ (%) | 98.0 ± 1.0 | 98.5 ± 0.7 | 98.8 ± 0.4 | 2.38 |
| $PaCO_2$ (kPa) | 5.1 ± 0.4 | 5.0 ± 0.3 | 5.0 ± 0.3 | 0.73 |
| $PaCO_2$ (mmHg) | 38.4 ± 2.8 | 37.7 ± 1.9 | 37.7 ± 2.4 | 0.73 |
| BCS | 5.6 ± 1.3 | 5.7 ± 1.2 | 6.0 ± 1.3 | 0.75 |

**Table 2** Results (mean ± standard deviation) of respiratory variables and isoflurane concentration in 32 lung-healthy dogs that received a tidal volume of 10 ($G_{10}$), 12 ($G_{12}$) or 15 ($G_{15}$) mL $kg^{-1}$ during controlled mechanical ventilation.

$f_R$, respiration rate; $P_{E'}CO_2$, end-tidal carbon dioxide; $V_T$ $kg^{-1}$, tidal volume to body weight ratio; $P_{E'}Iso$, end-tidal isoflurane.

§ Statistically significantly different to group 1, * Statistically significantly different to group 2, ♯ Statistically significantly different to group 3

| | **Tidal volume group** | | | |
|---|---|---|---|---|
| **Variables** | **$G_{10}$: 10 mL $kg^{-1}$** n = 10 | **$G_{12}$: 12 mL $kg^{-1}$** n = 11 | **$G_{15}$: 15 mL $kg^{-1}$** n = 11 | ***p*-value** |
| $f_R$ (breaths $minute^{-1}$) | 18 ± 5$^{\sharp}$ | 15 ± 6$^{\sharp}$ | 10 ± 3$^{\S *}$ | 0.002 |
| $P_{E'}CO_2$ (mmHg) | 37.8 ± 1.5 | 37.7 ± 1.2 | 36.6 ± 1.2 | 0.287 |
| $P_{E'}CO_2$ (kPa) | 5.0 ± 0.2 | 5.0 ± 0.2 | 4.9 ± 0.2 | 0.287 |
| $V_T$ $kg^{-1}$ (mL $kg^{-1}$) | 10.1 ± 0.4$^{*\sharp}$ | 12.0 ± 0.4$^{\S\sharp}$ | 15.3 ± 0.7$^{\S *}$ | < 0.001 |
| $F_{E'}Iso$ (%) | 1.1 ± 0.1 | 1.1 ± 0.1 | 1.1 ± 0.1 | 0.819 |

**Table 3:** Results of volumetric capnography and airway pressure variables (mean ± standard deviation) in 32 lung-healthy dogs that received a tidal volume of 10 ($G_{10}$), 12 ($G_{12}$) or 15 ($G_{15}$) mL $kg^{-1}$ during controlled mechanical ventilation.

$VD_{BE}$, Enghoff dead space; PIP, peak inspiratory pressure; MawP, mean airway pressure; $\dot{V}_E$, minute ventilation; $VTCO_{2,br}$, volume of expired $CO_2$ for one breath; $PACO_2$, partial pressure of alveolar carbon dioxide; $P\bar{E}CO_2$, mixed partial pressure of carbon dioxide.

§ Statistically significantly different to group 1, * statistically significantly different to group 2, ♯ statistically significantly different to group 3

| Variables | Tidal volume group | | | *p*-value |
|---|---|---|---|---|
| | **$G_{10}$: 10 mL $kg^{-1}$** n = 10 | **$G_{12}$: 12 mL $kg^{-1}$** n = 11 | **$G_{15}$: 15 mL $kg^{-1}$** n = 11 | |
| $VD_{BE}$ | 0.65 ± 0.07$^{\sharp}$ | 0.59 ± 0.06 | 0.54 ± 0.10$^{\S}$ | 0.008 |
| PIP ($cmH_2O$) | 11.1 ± 1.3$^{\sharp}$ | 10.8 ± 1.4$^{\sharp}$ | 13.0 ± 2.3$^{\S*}$ | 0.013 |
| MawP ($cmH_2O$) | 6.1 ± 0.3 | 6.0 ± 0.6 | 6.4 ± 0.5 | 0.121 |
| $VTCO_{2,br}$ (mL $breath^{-1}$) | 5.4 ± 2.5$^{\sharp}$ | 8.5 ± 4.6 | 10.8 ± 4.6$^{\S}$ | 0.017 |
| $\dot{V}_E$ (L $minute^{-1}$) | 4.76 ± 1.77 | 4.87 ± 1.33 | 3.86 ± 1.45 | 0.284 |
| $PACO_2$ (kPa) | 4.3 ± 0.2 | 4.4 ± 0.2 | 4.4 ± 0.2 | 0.442 |
| $PACO_2$ (mmHg) | 32.4 ± 1.7 | 33.1 ± 1.6 | 33.3 ± 1.5 | 0.442 |
| $P\bar{E}CO_2$ (kPa) | 1.76 ± 0.35$^{*\sharp}$ | 2.07 ± 0.27$^{\S}$ | 2.29 ± 0.40$^{\S}$ | 0.005 |
| $P\bar{E}CO_2$ (mmHg) | 13.20 ± 2.59$^{*\sharp}$ | 15.54 ± 2.01$^{\S}$ | 17.21 ± 3.03$^{\S}$ | 0.005 |

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